Patent
Attorney's Docket No. 000951-089

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Joseph B. PHIPPS	)	Group Art Unit: 3306
	)	
Application No.: 08/463,904	)	Examiner: M. Bockelman
	)	
Filed: June 5, 1995	)	
	)	
For: METHOD AND DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL	)	

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Joseph Bradley Phipps, hereby declare that:

1. I am a citizen of the United States of America residing in Maple Grove, Minnesota.

2. I received my undergraduate degree in Materials Science from University of Utah and my doctorate in Materials Science from Northwestern University.

3. I have been employed by Alza Corporation since 1991 and my current title is Director of Research E-Trans Technology and my responsibilities include performing research in materials science and electrotransport devices, particularly waveform parameters such as voltage, current and timing to enhance biocompatibility and drug flux.

4. I am the inventor of the above-identified patent application and I have reviewed the Official Action dated March 10, 1997, and I am familiar with the prior art cited in the Action.

5. The cited prior art does not teach my invention and does not recognize the surprising discovery which I have made. In particular, it is important to recognize that fentanyl is an extremely potent analgesic that is approximately 100 times stronger than morphine and 5-10 times stronger than hydromorphone. Sufentanil is even more potent and is approximately 15 times stronger than fentanyl. With such potent drugs requiring only microgram quantities, there is always the danger of overdoses. Therefore, an electrotransport system for delivery of those potent substances must provide safe transdermal administration.

It was well known at the time of my invention that diffusion of fentanyl and sufentanil substances through the skin was possible without the application of current, especially if the system were inadvertently applied to a skin site with compromised barrier function (e.g., abraded, scratched, sunburned, etc.). It was also well known at the time of my invention that the rate of diffusion of a substance across the skin could be decreased by decreasing the drug concentration. Accordingly, low concentrations have been desired to minimize diffusion (i.e., passive delivery) when an electrotransport device is not transmitting current to the skin. Furthermore, it is desired that the donor reservoir contain only the amount of drug needed for treatment of the patient to minimize the potential for inadvertent misuse or abuse of a "used" system.

To demonstrate that the prior art does not teach my invention, I can refer to the article by R. V. Padmanabhan et al entitled "*In Vitro* and *In Vivo* Evaluation of Transdermal Iontophoretic Delivery of Hydromorphone", a copy of which is attached as Appendix A. The article describes experiments involving the iontophoretic delivery of hydromorphone hydrochloride and indicates the delivery rate was independent of the concentration of hydromorphone in the donor solution over the range from 0.01M to 0.8M and states on page 130:

> Total depletion of the donor compartment should have occurred in approximately 18 hours, therefore the steady-state delivery of hydromorphone through pig skin was not significantly influenced until the donor solution concentration had dropped to about one millimolar.

In contrast to this teaching in the art, I have surprisingly found that the claimed concentrations of fentanyl and sufentanil in the donor reservoir are needed in order to achieve a drug flux that is independent of concentration for a given current. This discovery was especially surprising considering the research described in the Padmanabhan article, as well as the theoretical understanding existing at the time of my invention and to the present time. An often cited reference for the theoretical basis of electrotransport is the publication of G.B. Kasting and J.C. Keister entitled "Application of Electrodiffusion Theory For A Homogeneous Membrane to Iontophoretic Transport Through Skin", a copy of which is attached as Appendix B. The authors make theoretical predictions of the effect of donor drug concentration ~~drug concentration~~ on drug delivery efficiency (i.e., rate of drug delivery per unit current) for several cases. Their Case 1, beginning on page 202 develops the theoretical prediction for a drug salt with no added

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NaCl in the donor reservoir and normal saline on the receptor side of the in vitro cell. On page 204, they conclude that, for this case:

> ...the efficiency of drug delivery is largely determined by the ratio of drug diffusivity in the skin to that of the predominant counterion on the opposite side of the membrane. It is independent of drug concentration in this example.

This stated conclusion assumes a primarily aqueous transport pathway through skin which was well established at the time of my invention.

Furthermore, rather than having a donor reservoir that is designed to be fully depleted when administration is completed, my invention requires the concentration to be maintained substantially throughout the delivery period which means that administration is terminated even though a substantial amount of the drug still remains in the reservoir. Therefore, I believe that my invention is not disclosed or suggested anywhere in the cited prior art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

June 6, 1997
Date

Joseph B. Phipps